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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/593,316
Filing Date: June 13, 2000
Appellent(s): CLARK ET AL.

Salvatore J. Arrigo
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 9, 2006 appealing from the Office action mailed December 16, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The examiner disagrees with the summary of claimed subject matter contained in the brief on the following counts:

1. The appellant fails to "provide" claimed "ovine cells, tissues, and animals that have been engineered for reduction or elimination of the carbohydrate epitope Galα(1,3)Gal" as asserted (Brief, page 3, lines 1-

2). The attempt was failed at the time of the filing date. Thus, the claimed ovine cells, tissues, and animals do not exist.

2. The appellant fails to provide a live heterozygous α1,3GT gene knockout animal as implied (Brief, page 3, last paragraph, lines 3-5).

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

Upon further consideration, the following ground of rejection has been modified:

- Previous rejection of Claims 1-4 and 33-37 under 35 U.S.C. § 101, is withdrawn.
- Currently, Claims 5 and 6 stand rejected under 35 U.S.C. § 101; and Claims 1-6, 13-16, 33-37 stand rejected under 35 U.S.C. 112, first paragraph.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Denning et al, Nat Biotech 2001 June;19:559.

Yanagimachi, Mol Cell Endocrinol 2002;187:241-8.

Wells et al, Trends Biotechnol 2003:21:428-32.

Phelps et al, Science 2003 Jan;299:411-4.

Kuroiwa et al, Nat Genetics 2004;36:775-80.

Platt et al, Nat Biotech 2002 Mar;20:231-2.

Rhind et al, Nat. Biotechnology 2003;21:744-746.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101 & 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 6 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by a substantial utility, a well-established utility, and thus the asserted utility is not credible.

Appellant is referred to the Revised Utility Examination Guidelines published December 21, 1999 in the Federal Register, Volume 64, Number 244, pages 71441-71442 for the required *specific* and *substantial* utility. "A CLAIMED INVENTION MUST HAVE A SPECIFIC AND SUBSTANTIAL UTILITY. THIS REQUIREMENT EXCLUDES 'THROW-AWAY' 'UNSUBSTANTIAL',

OR 'NONSPECIFIC' UTILITIES," (column 3, 3rd paragraph of page 71441). In the instant case, the asserted specific utility of the claimed ovine animal is providing ovine cells and tissues suitable for xenotransplantation. Thus, the question is whether the asserted specific utility is substantial, well established, and credible.

In a recent decision, the court has explicitly interpreted how to meet the standard of a substantial utility (*In re Fisher*, 76 USPQ2d 1225 CA FC 2005). "COURTS HAVE USED THE LABELS 'PRACTICAL UTILITY' AND 'REAL WORLD UTILITY' INTERCHANGEABLY IN DETERMINING WHETHER AN INVENTION OFFERS A 'SUBSTANTIAL' UTILITY. INDEED, THE COURT OF CUSTOMS AND PATENT APPEALS STATED THAT "[P]RACTICAL UTILITY' IS A SHORTHAND WAY OF ATTRIBUTING 'REAL-WORLD' VALUE TO CLAIMED SUBJECT MATTER. IN OTHER WORDS, ONE SKILLED IN THE ART CAN USE A CLAIMED DISCOVERY IN A MANNER WHICH PROVIDES SOME *IMMEDIATE BENEFIT* TO THE PUBLIC" *NELSON*, 626 F.2D AT 856 (EMPHASIS ADDED). IT THUS IS CLEAR THAT AN APPLICATION MUST SHOW THAT AN INVENTION IS USEFUL TO THE PUBLIC AS DISCLOSED IN ITS CURRENT FORM, NOT THAT IT MAY PROVE USEFUL AT SOME FUTURE DATE AFTER FURTHER RESEARCH. SIMPLY PUT, TO SATISFY THE 'SUBSTANTIAL' UTILITY REQUIREMENT, AN ASSERTED USE MUST SHOW THAT THAT CLAIMED INVENTION HAS A SIGNIFICANT AND PRESENTLY AVAILABLE BENEFIT TO THE PUBLIC" (emphasis added).

Instant claims are drawn to ovine cells homozygous for inactivation of an α(1,3)GT gene, wherein the cells are obtained from an ovine animal homozygous for inactivation of an α(1,3)GT gene. The asserted utility of the animal and cells is to provide immunologically compatible animal tissue for xenotransplantation (Specification, page 6, line 15). Clearly, whether the claimed invention has a substantial utility very much depends on whether the claimed invention "IS USEFUL TO THE PUBLIC AS DISCLOSED IN

ITS CURRENT FORM", and whether "CLAIMED INVENTION HAS A SIGNIFICANT AND PRESENTLY AVAILABLE BENEFIT TO THE PUBLIC".

The instant specification provides isolated and novel sheep α1,3GT gene sequence, a vector construct for inactivating sheep α1,3GT gene, and a fibroblast cell whose genome comprising a single inactivated α1,3GT gene allele (heterozygous knockout). The specification established pregnancy via nuclear transfer cloning using said heterozygous knockout fibroblast cell as the donor nuclear material, and contemplates that an ovine animal heterozygous of α1,3GT gene could be produced at the end of the pregnancy, and used for crossbreeding.

However, none of the established fetuses were born alive, each died in utero. In the absence of a live lamb, crossbreeding is not possible since a fetus could not be used for breeding a viable lamb homozygous for α1,3GT inactivation. Further, it is not possible, from the heterozygous ovine fetus died in utero, to obtain cells homozygous for α1,3GT inactivation. Accordingly, the instantly claimed ovine animal or cells homozygous for α1,3GT inactivation were not materialized at the time of filing, not well established in the art, and could not have rendered a significant and presently available benefit to the public, and thus do not impart a substantial utility.

With respect to cells having *heterozygous* inactivation of α1,3GT gene, since α1,3GT gene is autosomal dominant, the ovine fetuses or ovine cells heterozygous for inactivation of α1,3GT gene would still express the Galα1,3Gal epitope and thus have no phenotype, i.e. they are not devoid of antibody-detectable Galα1,3Gal determinants. Thus, instantly disclosed heterozygous ovine fibroblast cell or fetus do not render a

significant and presently available benefit to the public, and does not impart a substantial utility.

As to the assertion that ovine cells having *heterozygous* inactivation of α1,3 GT gene could be used for knocking out the second allele of α1,3GT gene via homologous recombination in culture, although theoretically possible, has proven to be extremely difficult to achieve in the pertinent art, and at the time of instant filing it has yet to become reality for any species of *farm* animals (See discussion in Section 2, under 35 USC § 112, 1st paragraph, particularly the teachings of ***Phelps et al,*** Science 2003 Jan;299:411-4 and ***Kuroiwa et al,*** Nat Genetics 2004;36:775-80). To this end, post-filing publications on homozygous inactivation of a gene in cell culture of porcine (*Phelps et al*) and cattle (*Kuroiwa et al*) species have shown that further development of knockout technology is necessary. Thus, at the time of instant filing date, the technologies leading to the later success of obtaining a cultured cell having a homozygous knockout gene for porcine and cattle, and relied upon by the appellant, were not available and not routine in the art. Therefore, the claimed heterozygous cell does not render a significant and presently available benefit to the public, and does not impart a substantial utility.

For reasons set forth *supra*, it is concluded the claimed invention is not well-established, lacks a significant and presently available benefit to the public, and cannot be used to provide a well-defined, immediate, and particular benefit to the public. Accordingly, the claimed invention is not supported by a substantial asserted utility, a

well-established utility, and the credibility of the asserted specific utility could not be assessed.

Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Specifically, since the claimed invention is not supported by either a substantial, or a well established utility for the reasons set forth above and following, it would require undue experimentation for one skilled in the art intending to practice the claimed invention.

Claims 1-6, 13-16, and 33-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient

amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Claim 1 recites "Ovine tissue devoid of antibody-detectable Gal α (1,3)Gal determinants", claim 3 recites "isolated ovine cell or tissue that expresses glycosyl transferase enzymes but does not detectably express α(1,3)GT", claim 4 recites "an ovine cell which is heterologous or homozygous for inactivation of an α(1,3)GT gene", claim 6 recites "an ovine animal that is homozygous for inactivation of an α1,3GT gene". Dependent claims 2, 33-37 specify various types of cells inactivated for an α1,3GT gene.

As an initial matter, the claimed somatic cell homozygous for inactivation of an α1,3GT gene has not been exemplified by the specification, nor an embryonic stem cell lacking one or two allele(s) of an α1,3GT gene could have been provided by the specification, because sheep ES cells were not available and yet to be identified at the time of the effective filing date. Further, it should be noted if fertilized eggs are used in the claimed process, they won't divide sufficient number of times to allow the selection process (30 to 45 times of division are required for selection).

Since the claimed cells and animals homozygous for inactivation of an α(1,3)GT gene (α(1,3)GT-/-), tissue and organs devoid of Gal α (1,3)Gal determinants have not been reduced to practice at the time the application was filed, further consideration is necessary of cloning methods provided by the specification and the state of the art at the time of the effective filing date.

Claim 13 is directed to producing an ovine animal that is homozygous for inactivation of an α1,3GT gene comprising providing an ovine embryo of cells heterozygous or homozygous for inactivation of an α1,3GT gene, engrafting the embryo into the uterus, birth an ovine, and further mating the ovine if the birthed ovine has only one inactivated allele of α1,3GT gene (α1,3GT+/-). The practice of methods of claims 14 and 15 relies on the realization of claim 13, i.e. the availability of an α(1,3)GT-/- ovine animal.

The following is an analysis of the enablement or lack thereof for the claimed invention.

1. Producing claimed α(1,3)GT-/- ovine animal by crossbreeding an α(1,3)GT+/- ovine animal has not exemplified.

Claim 13 states, "providing an ovine embryo of cells according to claim 4", and claim 4 encompasses cells both heterozygous or homozygous for inactivation of an α1,3GT gene. Since the later has not been reduced to practice, only heterozygous knockout cell could be used at the time of instant filing. Claim 13 continues, "engrafting the embryo into the uterus of a female, birthing an ovine with an inactivated α1,3GT gene from the engrafted female, and if the birthed ovine has the α1,3GT gene inactivated on only one allele, then mating it with another ovine with an inactivated α1,3GT gene, thereby producing an ovine that is homozygous for inactivation of the α1,3GT gene".

In the specification, the appellant provides an ovine embryo of cells heterozygous for inactivation of an α1,3GT gene, reduces to engraft the embryo into a uterus of a

sheep host. However, at the time of the effective filing date, none of the lambs comprising the *heterologous* inactivation of α1,3GT gene were born alive. In fact, each died in utero. Thus, the α1,3GT+/- lamb, the starting material for crossbreeding, is missing, one cannot mate a heterozygous fetus to obtain a sheep devoid of Gal α (1,3)Gal determinants. In view of the disclosure, the enablement of instantly claimed invention very much depends on the state of the prior art.

In view of the state of the art in somatic NT cloning at the time, the art was still under-developed and many known or unknown barriers hamper the success. For example, a post-filing publication by the appellant (*Denning et al*, Nat Biotech 2001 June;19:559) teaches the difficulties of somatic cell targeting, "A SUBSTANTIAL NUMBER OF COLONIES WITH ONLY TARGETED CELLS SENESCED BEFORE THEY COULD BE PREPARED FOR NUCLEAR TRANSFER. THE HIGH ATTRITION RATE OF TARGETED CLONAL POPULATIONS SUITABLE FOR NUCLEAR TRANSFER REPRESENTS ONE OF THE MAJOR HURDLES OF GENE TARGETING IN PRIMARY SOMATIC CELLS" (left column, page 560, emphasis added). The general state of the art was such that somatic NT cloning in farm animals was and still is highly inefficient, and the underlying mechanism for such inefficiency had not been fully understood, which reflects the under-developed state of the art, and such inefficiency cannot be resolved by routine experimentation. *Yanagimachi* (Mol Cell Endocrinol 2002;187:241-8) teaches, at a post-filing date, that "CLONING EFFICIENCY-AS DETERMINED BY THE PROPORTION OF LIVE OFFSPRING DEVELOPED FROM ALL OOCYTES THAT RECEIVED DONOR CELL NUCLEI-IS LOW REGARDLESS OF THE CELL TYPE (INCLUDING, EMBRYONIC STEM CELLS) AND ANIMAL SPECIES USED. IN ALL ANIMALS EXCEPT OF JAPANESE BLACK BEEF CATTLE, THE VAST MAJORITY OF CLONED EMBRYOS PERISH BEFORE REACHING FULL TERM" (Abstract), and "THUS FAR, CLONED OFFSPRING

THAT SURVIVED BIRTH AND REACHED ADULTHOOD WERE THE EXCEPTION RATHER THAN THE RULE (page 243, left column, emphasis added). *Yanagimachi* goes on to teach, "THIS LOW EFFICIENCY OF CLONING SEEMS TO BE DUE LARGELY TO FAULTY EPIGENETIC REPROGRAMMING OF DONOR CELL NUCLEI AFTER TRANSFER INTO RECIPIENT OOCYTES. CLONED EMBRYOS WITH MAJOR EPIGENETIC ERRORS DIE BEFORE OR SOON AFTER IMPLANTATION" (abstract). *Wells et al* (Trends Biotechnol 2003:21:428-32) teach that the continuous loss of clones throughout pregnancy and high mortality during the perinatal period raise serious animal welfare concerns and these losses can mostly be attributed to faulty epigenetic reprogramming of the donor cell genome, resulting in major dysregulation of gene expression (paragraph bridging left & right column in page 1). In light of the state of the prior- and post-filing art *supra*, the outcome of instant working examples does not appear to be just a random incidence because the skilled artisans teach that fetuses not surviving to term often reflect the real difficulty and major challenge in somatic cell NT cloning.

Thus, in light of the state of the art and the levels of the skilled, the lack of survival to term in appellant's α1,3GT+/- ovine fetuses is less likely an accident, but reflects real challenges attributed to faulty epigenetic reprogramming and major genetic dysregulation. MPEP teaches, "WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03) The court states, "IF INDIVIDUALS OF SKILL IN THE ART STATE THAT A PARTICULAR INVENTION IS NOT POSSIBLE YEARS AFTER THE FILING DATE, THAT WOULD BE EVIDENCE THAT THE DISCLOSED INVENTION WAS NOT

POSSIBLE AT THE TIME OF FILING AND SHOULD BE CONSIDERED. IN *IN RE WRIGHT*, 999 F.2D 1557, 1562, 27 USPQ2D 1510, 1513-14 (FED. CIR. 1993). Accordingly, taking as a whole the state of the art, the levels of the skilled in the art, the disclosure of the specification, and the lack of live heterozygous ovine animals, it is reasonable to doubt the enablement of instant claims.

Claims 14 and 15 are directed to obtaining ovine cells and tissues from an ovine animal having disruption of both alleles of an α1,3GT gene, the method is not enabled because as indicated *supra*, the starting material (i.e. the α1,3GT+/- ovine animal), thus the basis for harvesting the cells and organs is lacking.

2. Producing a somatic ovine cell homozygous for inactivation of α1,3GT gene in culture has not been evidenced.

The specification contemplates, alternatively, cells having a heterozygous knockout can be targeted with an inactivation vector to inactivate α1,3GT gene on the other haplotype to generate homozygous knockout cells and embryo inactived on both alleles of the α1,3GT gene (Specification, page 41, lines 17-20). The specification fails to actually provide such cell at the time of instant filing.

Turning to the state of the art pertaining to making homozygous knockout cells, difficulties exist in both gene targeting and targeted cell selection processes. For example, somatic cells prepared for nuclear transfer are difficult to sustain *in vitro* due to their innate viability. *Denning et al* (Nat Biotech 2001;19:559-562) teach, "A SUBSTANTIAL NUMBER OF COLONIES WITH ONLY TARGETED CELLS SENESCED BEFORE THEY COULD BE PREPARED

FOR NUCLEAR TRANSFER. THE HIGH ATTRITION RATE OF TARGETED CLONAL POPULATIONS SUITABLE FOR NUCLEAR TRANSFER REPRESENTS ONE OF THE MAJOR HURDLES OF GENE TARGETING IN PRIMARY SOMATIC CELLS" (left column, page 560).

As to targeting the second allele of a heterozygous gene *in vitro*, the skilled artisans have shown repeatedly that this had been extremely difficult to accomplish. The state of the art has been illustrated in two of the post-filing publications submitted by the appellant, i.e. ***Phelps et al***, Science 2003 Jan;299:411-4, and ***Kuroiwa et al,*** Nat Genetics 2004;36:775-80; both pointed to evidence **contrary to** the appellant's assertion that claimed method is enabled for producing homozygous knockout cells in culture. When taking the experience of these skilled artisan as a whole with the appellant's disclosure, it is reasonable to conclude it requires further development of the art (undue experimentation) to provide a homozygous knockout ovine cell.

Phelps et al, who describe making pig cells homozygous for α1,3GT inactivation, teach, "ALTHOUGH OUR INTENT WAS TO KNOCK OUT THE SECOND ALLELE OF THE α1,3GT GENE BY HOMOLOGOUS RECOMBINATION, THIS DID NOT OCCUR" (lines 1-4, right column, page 413, emphasis added). The statement confirms the difficulty and unpredictability of double knock-out a gene in a somatic cell. In the publication, *Phelps et al* employed a new method for selecting α1,3GT-double negative cells, i.e. a "toxin A selection" method, which is critical in achieving the goal of obtaining a porcine cell homozygous for inactivated α1,3GT gene. *Phelps et al* teach, "THE FACT THAT ONE NORMAL-SIZED ALLELE WAS OBSERVED (INSTEAD OF TWO SHORTER KNOCKOUT ALLELES) INDICATED THAT KNOCKOUT OF THE SECOND α1,3GT ALLELE WAS DUE TO MECHANISMS OTHER THAN TARGETED HOMOLOGOUS

RECOMBINATION-MEDIATED DISRUPTION, PROMOTER DYSFUNCTION, OR MRNA MISSPLICING AND INSTABILITY" (mid- and right column, page 412). Apparently, *Phelps et al* failed to knockout the second allele of the porcine α1,3GT gene in a somatic cell using instantly claimed, conventional targeted homologous recombination-mediated disruption, but relied on selection of a natural mutation on the second allele of the porcine α1,3GT gene. *Phelps et al* went on to teach "BECAUSE WE USED THIS POWERFUL SELECTION METHOD, WHICH ALLOWS US TO ISOLATE ANY EVENT THAT RESULTS IN LOSS OF α1,3GT ACTIVITY, WE DISCOVERED A MUTATION IN THE SECOND ALLELE OF THE α1,3GT GENE. HAD WE USED STANDARD SELECTION METHODS WITH PUROMYCIN OR HYGROMYCIN, WE WOULD NOT HAVE FOUND THE MUTATION" (right column, page 413, emphasis added). The *Phelps* publication confirms the difficulty of double knockout a gene in a somatic cell, which has not been resolved using routine experimentation even long after instant priority date.

Another post-filing reference cited by the appellant during instant prosecution is *Kuroiwa et al* (Nat Genetics 2004;36:775-80), who gave a clear view regarding the state of the art in gene targeting of somatic cells in culture for NT cloning. *Kuroiwa et al* teach, "GENE TARGETING IN SOMATIC CELLS VERSUS EMBRYONIC STEM CELLS IS A CHALLENGE; CONSEQUENTLY, THERE ARE FEW REPORTED SUCCESSES AND NONE INCLUDE THE TARGETING OF TRANSCRIPTIONALLY SILENT GENES OR DOUBLE TARGETING TO PRODUCE HOMOZYGOTES" (see e.g. abstract, emphasis added). *Kuroiwa et al* teach breeding to homozygosity is severely impeded in species that have a long generation interval, such as cows, sheep and pigs, further they are negatively impacted by the consequences of inbreeding. *Kuroiwa et al* particularly mentioned "innovative" approaches to obtain homozygous α (1,3)GT

knockout pigs as reported by *Phelps et al*, but pointed out "UNFORTUNATELY, THESE APPROACHES ARE NEITHER USEFUL FOR SILENT GENES NOR WIDELY APPLICABLE FOR ACTIVE GENES" (right column, page 775). The success of *Kuroiwa et al* was brought about by another innovative approach, i.e. sequential application of gene targeting by homologous recombination and rejuvenation of cell lines by cloned fetuses. Such approach was developed long after the instant filing date, and the specification fails to teach such a method, thus, the reference does not support the enablement of instant claimed invention. To the contrary, it confirms that it requires further development and undue experimentation to enable the instantly claimed invention.

The specification fails to teach how to overcome the difficulties as taught by *Denning et al*, it fails to teach the innovative methods as taught by *Phelps et al* and *Kuroiwa et al*, thus, the success of *Phelps et al* and *Kuroiwa et al* do not support the enablement of the claimed invention at the time the application was filed. In *In re Glass*, the appellant attempted to use the disclosures of four patents issued after his filing date, and court ruled, "IF INFORMATION TO BE FOUND ONLY IN SUBSEQUENT PUBLICATIONS IS NEEDED FOR SUCH ENABLEMENT, IT CANNOT BE SAID THAT THE DISCOSURE IN THE APPLICATION EVIDENCES A COMPLETED INVENTION... IT IS AN 'S OBLIGATION TO SUPPLY ENABLING DISCLOSURE WITHOUT RELIANCE ON WHAT OTHERS MAY PUBLISH AFTER HE HAS FILED AN APPLICATION ON WHAT IS SUPPOSED TO BE A COMPLETED INVENTION", "IF HE CANNOT SUPPLY ENABLING INFORMATION, HE IS NOT YET IN A POSITION TO FILE. The specification fails to teach how to overcome the art known hurdles in knocking out the second allele of a ovine cell in culture, it fails to teach the innovative methods found in the post-filing art, and thus it fails to provide an enabling disclosure for instantly claimed invention.

In conclusion, knocking out the second allele of the sheep α1,3GT gene via homozygous recombination-mediated disruption in a heterozygous ovine somatic cell was not routine in the art, had not reduced to practice, and had not been achieved in any species of farm animals at the time of instant filing, and it would have required undue experimentation for the skilled intending to practice the claimed invention.

3. Solving the problem of hyperacute rejection does not make xenotransplantation feasible.

It is well known in the art that Gal(1,3)Gal determinant is the major antigen responsible for hyperacute rejection response in xenotransplantation. Claim 16 is drawn to a method of xenotransplantation using ovine tissue devoid of antibody detectable Gal(1,3)Gal determinants, in other words, using tissue generated from ovine animals having homozygous knockout of the α1,3GT gene for transplantation in humans. As discussed foregoing, the specification fails to provide sufficient guidance or reduce to practice to provide the claimed ovine homozygous for α1,3GT gene inactivation, thus, the starting material for the claimed xenotransplantation method is lacking.

Even assuming *arguendo* that claimed homozygous knockout ovine animals are readily available to the public, it would not render the xenotransplantation feasible because the tissue or organ devoid of antibody detectable Gal(1,3)Gal determinants will still face vigorous host rejection response when used in xenotransplantation. This is because Gal(1,3)Gal determinant is only one of the many factors that trigger xenograft rejection responses. *Platt et al* (Nat Biotech 2002 Mar;20(3)231-2) clearly teach,

"UNFORTUNATELY, SOLVING THE PROBLEM OF HYPERACUTE REJECTION DOES NOT MAKE XENOTRANSPLANTATION FEASIBLE, BUT RATHER REVEALS A MORE VEXING PROBLEM CALLED ACUTE VASCULAR REJECTION. ACUTE VASCULAR REJECTION, LIKE HYPERACUTE REJECTION, IS TRIGGERED BY ANTI-DONOR ANTIBODIES; HOWEVER, IN CONTRAST TO HYPERACUTE REJECTION, THESE ANTIBODIES ARE NOT DIRECTED EXCLUSIVELY AGAINST α1,3GAL, AND THE INVOLVEMENT OF THE COMPLEMENT SYSTEM IS FAR MORE SUBTLE" (Emphasis added). In view of such knowledge, the claimed method does not appear to be enabled in the absence of evidence to the contrary.

Therefore, it is apparent at the time of the invention, the animal cloning practitioner, while acknowledging the significant potential of somatic cell nuclear transfer cloning, still recognizes that such practice was neither routine nor accepted, and awaits significant development and guidance for its practice. Therefore, it is incumbent upon appellant to provide sufficient and enabling teachings within the specification to support the claimed invention. Here, the general knowledge and levels of skill in the art do not supplement the omitted disclosure, given the inefficiency in farm animal somatic NT cloning, and given the constant failure in knocking out the second gene allele of a heterozygous ovine cell. Although the instant specification provides sheep cells having heterozygous inactivation of α1,3GT gene and fetuses, it is not enabled for the claimed invention because the specification fails to provide sufficient and specific guidance for the skilled artisan to reliably and routinely produce what is now claimed. In summary, the teachings and guidance present in the specification, as a whole, represent an initial investigation into the feasibility of developing a useful means for producing ovine

animals devoid of Galα1,3Gal determinants, which awaits further development to practical levels.

Accordingly, in view of the limited guidance, the lack of predictability of the art and the nature and breadth of the claims, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

(10) Response to Argument

Appellant's arguments would be addressed in the order in which they presented in the appellant's appeal brief, and repetitive arguments would be addressed together as a group.

Appellant first acknowledged that the genetically modified stem cells used in making α1,3GT knockout mice is not amenable to making knockout sheep, but argued that technology for making the sheep was well-established at the time of filing, and efforts to make α1,3GT pigs were already under way. Appellant then asserted the latchkey that enables knockout sheep to be made is the sheep [α1,3GT] sequence, and no legal requirement that an actual working example be provided in the specification (Brief, page 5, 1st & 2nd paragraphs, and page 7).

In response, it is noted that throughout the appellant's brief, a recurring argument is alleging that instant enablement rejection is based on the lack of a working example. The examiner disagrees with the allegation. To the contrary, the basis for the lack of enablement rejection is not a single factor such as lacking a working example, but a comprehensive assessment of the state of the prior art, the levels of the skilled in the

art, the nature of the claims, and the guidance provided along with the inability to obtain a live α1,3GT+/- ovine animal or an ovine cell inactivated on both alleles of the α1,3GT gene *even though* working examples do exist in the specification.

Appellant is reminded that the asserted "well-established" technology has met with extremely low efficiency in cloning outcome, and the post-filing date report on making α1,3GT knockout pigs (*Phelps et al*) has evidenced that neither the "well-established" technology nor the availability of the pig α1,3GT sequence, made the knockout of the second allele possible via homologous recombination-mediated disruption. In fact, the experience in making the α1,3GT knockout pigs supports that it requires further development in somatic cell NT cloning technology to see the eventual success of making α1,3GT-/- pigs, which was not through the conventional homologous recombination-mediated disruption as taught in the instant specification.

The teaching of *Denning et al, Phelps et al, Kuroiwa et al* also speaks volume in supporting the Office position for non-enablement of the claimed invention as detailed in the body of the rejection. Again, the question raised is not simply due to lack of working examples as asserted by the appellant (Brief, page 5, 3rd paragraph) but the inability to make what the appellant set out to accomplish in the existing working examples.

The appellant then attributes the inability to obtain claimed cells and animals to lack of funding, comparing the situation to requiring clinical trial in humans for a pharmaceutical citing *In re Branna*. The appellant assert they should not be denied patent coverage just because a homozygous knockout sheep was not obtained, and the

appellant should not be penalized for disclosing their invention before they completed reduction to practice of all the embodiments (Brief, 3rd paragraph, page 5-page 6).

In response, "a homozygous knockout sheep was not obtained" is only one of the reasoning/basis for the conclusion of lacking enablement (see detailed analysis in the rejection under § 112, 1st paragraph). Instant situation is not analogous to *In re Branna*, where a compound has been made and tested in animals. The appellant is seeking a patent monopoly for things that have yet to be made, and the state of the art points to hurdles in practicing the claimed invention that cannot be resolved by routine experimentation. The appellant is reminded, in *Brenner v. Manson*, 148 USPQ 689, 696 (US SupCt., 1966), the court indicated,

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

In the instant case, the claimed animals and cells are yet to be produced, and the claimed process awaits further refinement and development to the point-where they can bring specific benefit in currently available form to the public. Accordingly, the instant disclosure as filed fails to meet the statutory patentability requirement under 35 USC § 101 and § 112, 1st paragraph.

Rejections under 35 USC § 112, 1st paragraph.

In the Appeal Brief, the appellant first argues "**Sheep cells having an inactivated α1,3GT gene allele can readily be produced**" (page 8, heading 1).

In response, making heterozygous ovine cells with one α1,3GT gene allele being inactivated has not been an issue under the enablement rejection. The issue is whether one can readily prepare an ovine cell or animal for *homozygous* inactivation of α1,3GT gene (knocking out both alleles) starting from the heterozygous knockout cell.

To this end, the appellant argues they provided new sheep α1,3GT gene and targeting sequence, and methods for using gene sequences to inactivate the corresponding gene in living cells are described extensively in the art.

In response, the instant claims are not drawn to the α1,3GT gene sequence or construct, the claims under current examination are drawn to ovine cells and animals having homozygous knockout of α1,3GT gene, making such does not appear to be routine experimentation for reasons set forth on record and *supra*. This could also be seen in appellant's disclosure and post-filing publications.

In the specification, different genetic constructs were used for targeting fibroblast cells of different sheep species. Only one allele of α1,3GT gene was successfully inactivated in fibroblast cells of FD sheep with a construct targeting exon 4 of α1,3GT gene. Similar attempts failed targeting cells of black Welsh mountain sheep or using a construct targeting exon 8 of α1,3GT gene (examples 4-6). Although knocking out any one exon of the gene may be sufficient, the observation shows the attempt has not always successful, or encountered more failure than success. Subsequently, using

nuclear transfer technology, ten recipients were determined to be pregnant, but the specification is silent concerning the fate of the pregnancy (example 6).

In a post-filing publication submitted in IDS (*Denning et al,* Nat Biotech 2001 June;19:559), the appellant discloses that 35 pregnancies were produced, the oldest fetuses died *in utero* at 118 and 130 days (term 148 days), and no live birth was obtained (page 560, right column). Apparently, the claimed cells, tissue, organs, and animals comprising a disruption of both alleles of the α1,3GT gene have not been reduced to practice as of the effective filing date. As the appellant rightfully concluded in the 2001 publication, "THE HIGH ATTRITION RATE OF TARGETED CLONAL POPULATIONS SUITABLE FOR NUCLEAR TRANSFER REPRESENTS ONE OF THE MAJOR HURDLES OF GENE TARGETING IN PRIMARY SOMATIC CELLS".

In the footnotes, the appellant presented arguments to certain positions of the Office during the course of the prosecution, the arguments are moot since the positions are not current ground for the enablement rejection.

The appellant then asserts "**Sheep cells that are homozygously inactivated at α1,3GT locus can readily be produced**" (page 9, heading 2).

In response, a detailed analysis and reasoning why the Office disagrees with the above assertion has been given as set forth in sections 2 of the enablement rejection (pages 13-16 of the Answer), and will not be reiterated.

The appellant listed three ways of making ovine cells and animals homozygous for α1,3GT inactivation (Brief, page 10).

With respect to the first two methods listed, the specification teaches selection for the homozygous knockout using a drug resistance gene such as neomycin. Similarly, two constructs with two different drug resistance genes could also be used for selection (Specification, page 40, line 24 to page 41, line 2). This is summarized in the Appeal Brief as **a**). Using a step-wise increase in antibiotic concentration to knockout both alleles, and referring to U.S. P. 5,589,369 for support; and **b**). Using two different antibiotics to sequentially knockout each allele.

In response, the two antibiotics selection methods, whether it is the one step or two-step selection, the methods are considered "standard selection method" as referred to by *Phelps et al*, and *Phelps et al* clearly teach that such standard selection method would not reveal the mutation in the second allele or identify the possible presence of cells having homozygous inactivation of the α1,3GT gene.

With respect to US 5,589,369, the appellant alleges the examiner has not explained why the making of α1,3GT knockout cells would pose special difficulties that prevent the method of the '369 patent from being implemented as a matter of routine experimentation (Brief, page 11, 1st paragraph).

In response, the appellant's attention is directed to page 14 of the Office action mailed January 30, 2004, where the examiner clearly indicated the cited patent is not a somatic cell cloning patent but directed to genetic modification of *mouse embryonic stem cells.* The ES cell for ovine has not been identified, thus the method taught by '369 patent does not apply to making the sheep.

With respect to the third, antibody selection method, the specification teaches, "*homozygous knockout cells can be made by targeting the other allele in the donor cells using a knockout vector, and selecting cells deficient in the particular surface antigen*". In footnote 3, Appellant asserts that an antibody selection method is the equivalent to the toxin A method used by *Phelps et al*. However, the *Phelps* method is selecting for a gene recombination event, whereas the antibody selection is determining on a protein expression event, thus, the two could not be the equivalent.

Moreover, all three of aforementioned methods require retargeting and selecting for homozygous knockout cells, the general consent in the art and the experience of *Phelps et al* have shown this has been extremely difficult to achieve (See discussion in the body of the § 112, 1st paragraph).

The appellant then concluded that "*the claims have been rejected under 35 USC § 112, 1st paragraph on the assertion that a α1,3GT knockout sheep cannot be made*" (e.g. 3rd paragraph, page 10 of the Brief). This is not the case. The Examiner has clearly indicated in the Office action issued 12/2004,

> While, the intent for citing the numerous references contradicting the s assertion is not to say that cloning by nuclear transfer to generate an ovine having homozygous inactivation of the α1,3GT gene can never be achieved, the intent is to provide art taught reasoning as to why the instant claims are not enabled at the time of the filing, and to illustrate the general state of the art in cloning, particularly nuclear transfer cloning to properly determine whether additional and specific guidance should be provided by the specification.

The best way to conclude this argument should be the appellant's own words, *Denning et al* (Cloning & Stem Cells 2001;3:221-31), reporting results including instant investigation, teaches "SIGNIFICANT CHALLENGES, SUCH AS ESTABLISHMENT OF SOMATIC GENE

TARGETING TECHNIQUES, MUST BE OVERCOME BEFORE THE TECHNOLOGY CAN BE APPLIED ROUTINELY" (abstract), "WE EXPERIENCED SIGNIFICANT PROBLEMS IN ISOLATING POPULATIONS THAT COULD BE USED FOR NT" (last paragraph, page 229), "THEREFORE, IT IS DIFFICULT TO IMAGINE HOW IT WILL BE POSSIBLE TO ISOLATE SUCH LINES FROM NORMAL PIG FIBOBLASTS SUCH AS THESE WITH THE FREQUENCIES OF GENE TARGETING THAT WE REPORT" (1st paragraph, page 230), and "THERE IS CLEARLY A NEED TO OPTIMIZE AS WELL AS DEVELOP NEW APPROACHES IN BOTH SPECIES" (last paragraph, page 230).

In the Appeal Brief, appellant asserts "**Animals having an homozygously inactivated at α1,3GT locus can readily be made from inactivated donor cells by nuclear transfer**" (page 11, heading 3).

The arguments in this section is essentially that nuclear transfer technology has created Dolly the sheep, and thus has been fully described and enabled citing U.S. Patents 6,147,276 and 6,252,133 .

In response, it is noted the technology for making farm animal cloning have undergone significant development, new techniques and knowledge have emerged since the cited *Campbell and Wilmut* patents, without such progress, the homozygous pig disclosed by *Phelps* or the cattle disclosed by *Kuroiwa et al* would not have been obtained. To this end, in addition to the state of nuclear transfer technology illustrated by the teachings of *Denning et al* and *Yanagimachi et al* as cited *supra*, *Dr. Rhind and Wilmut* (Nat Biotech 2003;21:744-6), the co-inventor of Dolly the sheep, teaches at the conclusion of a pathological investigation of cloned lambs, "IN CONTRAST TO THE OPINION

THAT THE MAJORITY OF CLONED ANIMLS ARE 'SEEMINGLY HEALTHY', WE PROVIDE HERE AN ALTERNATIVE VIEW ON THE BASIS OF A DETAILED PATHOLOGICAL STUDY OF A GROUP OF CLONED LAMBS THAT WERE NOT VIABLE AFTER BIRTH. OUR ANALYSIS REVEALS NEW EVIDENCE OF A SERIES OF CLONING-RELATED ABNORMALITIES (SUMMARIZED IN TABLE 1)" (1st paragraph, page 744). *Dr. Rhind and Wilmut* went on to teach, "THE RESULTS ALSO EMPHASIZE THE NEED FOR BASIC STUDIES ON SOMATIC CELL REPROGRAMMING TO IMPROVE SUCCESS RATES AND REDUCE NEONATAL DEATHS IN CLONED ANIMALS" (last paragraph, page 745). Apparently the high rate of *in utero* death was not just an accident, it reflected underlying mechanism that needs to be addressed before one reach the point of routine somatic cell NT cloning.

Further, Dolly is not generated from a *genetically modified* somatic cell, even though the appellant states there is no reason to believe that genetically altering the donor cell would affect its suitability as a nuclear donor, genetic modification adds challenge to the cloning process, such as seen in the failed attempts to knockout the second allele of the a 1,3GT gene. As a result, the claimed invention requires the combination of somatic cell cloning and genetic modification, each may contribute to the failure of instantly claimed invention as a whole, which does not appear to be resolved by routine experimentation at the time of instant priority date.

The appellant then cited numerous publications to support his position; the cited references have following features:

- Most of the cited references are not drawn to knockout animals,
- All of the cited references are directed to either different animal species, or different genes, and each success has a unique story.

- Out of 12 references cited, only two references are published *before* instant effective filing date, both of which are drawn to a transgenic but not knockout animal (Schnieke et al, and Cibelli et al).

For example, ***Uchida et al*** reference is a post-filing art, drawn to a transgenic miniature pig, not a knockout sheep. Without going into the details, *Uchida et al* stated at the post-filing date, "THIS STUDY IS THE FIRST SUCCESSFUL REPORT CONCERNING THE PRODUCTION OF TRANSGENIC MINIATURE PIG BY PRONUCLEAR MICROINJECTION" (abstract), which illustrated the state of the art, i.e. successful production of transgenic miniature pig by pronuclear microinjection has not yet been achieved at the time of instant priority date, and that it is not routine in the art to produce the claimed invention. ***Bondoli et al*** is a post-filing date reference, drawn to transgenic pigs, not a knockout sheep. ***Lai et al*** reference is a post-filing date art, drawn to a transgenic pig, not a knockout sheep. ***McCreath et al*** is a post-filing date reference describing the efficiency of reproductive gene insertion in sheep, not a knockout sheep. Without going into the details, *McCreath et al* also stated at the post-filing date, "THE GENE TARGETING HAS NOT YET BEEN ACHIEVED IN MAMMALS OTHER THAN MICE", which again illustrated that it is not routine in the art to produce the claimed invention. ***Dai et al,*** reported at a post-filing date a knockout *pig* that is *heterozygous* for α (1,3)GT gene, not homozygous sheep. ***Denning et al*** describes instant invention at a post-filing date. *Denning et al* obtained live birth of sheep having a deletion in PrP gene but not those having a deletion in α (1,3)GT gene. This indicates that cloning efficiency differs between cloned sheep having different target genes and the targeting gene might be relevant to the success of reproductive

cloning. ***Schnieke et al*** and ***Cibelli et al*** describe transgenic sheep or calves, not knockout sheep. As for the ***Ramsoondar*** reference, they reported using a specific construct targeting a *specific* region of the α (1,3)GT gene of the cattle, and as of the publication date (4 years after the instant effective filing date), only heterozygous knockout was achieved. Assuming a homozygous knockout of the α (1,3)GT gene in cattle could be achieved later, the specific method which leads to the success was not taught in the instant disclosure. Likewise, more than four years after the effective filing date, ***Sendai et al*** reported the *first* success of *heterozygous* disruption of the α (1,3)GT gene in cattle. It is noted the genetic background differs among sheep, pig, and cattle. As indicated in the specification, pig and sheep share 90% and 82% homology in nucleic acid and amino acid sequences respectively (Specification, table 1). Although these may not be huge differences, the fact is what has been achieved in pigs and cattle at a post-filing date has not been achieved in sheep even though attempts have been made in altering α (1,3)GT gene in sheep by highly skilled in the art.

As for ***Kuroiwa et al*** who reported a sequential gene targeting method for making homozygous Ig-μ gene knockout cattle. *Kuroiwa* reference deserves attention because they gave a clear view regarding the state of the art in animal cloning. *Kuroiwa et al* teach, "GENE TARGETING IN SOMATIC CELLS VERSUS EMBRYONIC STEM CELLS IS A CHALLENGE; CONSEQUENTLY, THERE ARE FEW REPORTED SUCCESSES AND NONE INCLUDE THE TARGETING OF TRANSCRIPTIONALLY SILENT GENES OR DOUBLE TARGETING TO PRODUCE HOMOZYGOTES" (emphasis added). *Kuroiwa et al* teach breeding to homozygosity is severely impeded in species that have a long generation interval, such as cows, sheep

and pigs, further they are negatively impacted by the consequences of inbreeding. *Kuroiwa et al* particularly mentioned "innovative" approaches to obtain homozygous α (1,3)GT knockout pigs as reported by *Phelps et al*, but pointed out "UNFORTUNATELY, THESE APPROACHES ARE NEITHER USEFUL FOR SILENT GENES NOR WIDELY APPLICABLE FOR ACTIVE GENES" (right column, page 775). The success of *Kuroiwa et al* was brought about by another innovative approach, i.e. sequential application of gene targeting by homologous recombination and rejuvenation of cell lines by cloned fetuses. Such approach was developed long after the instant filing date, and the specification fails to teach such a method, thus, the reference does not support the enablement of instant claimed invention. To the contrary, it confirms that it requires further development and undue experimentation to enable the instantly claimed invention.

From above analysis, it has become apparent that appellant has constantly rely on post-filing date references as support for enablement of the instant claimed invention. In the instant case, appellant heavily relied on α (1,3)GT null pigs that become available four years after the instant filing date for enablement of the claimed invention on sheep. However, none of the post-filing success in α (1,3)GT null pigs could be achieved in the absence of further advance in knowledge and technology of animal cloning that become available after instant filing date. Thus, judged as of the filing date, the instant disclosure is insufficient to provide enablement for what is claimed.

In the Appeal Brief, the appellant asserts "**Animals that homozygous for inactivated α1,3GT can readily made**" (Brief, page 14, heading 4).

The appellant reiterated three different ways of making the α1,3GT-/- animal, which have been addressed in the rejection supra, and will not reiterated.

The appellant then asserts the only relevant question in relation to the invention claimed is whether knocking out both α1,3GT alleles would somehow compromise the viability of the animal.

In response, this is not one of the grounds for enablement rejection currently on record, and thus the arguments are moot.

It is noted nevertheless that although homozygous knockout of α1,3GT may not compromise the viability of the animal, the faulty epigenetic reprogramming of donor cell genome during somatic cell NT cloning process often results in major dysregulation of gene expression and death of the cloned animals.

In the Appeal Brief, the appellant asserts "**Cells from homozygous knockout animals will have cells and tissues lacking the Galα1,3Gal xenoantigen**" (Brief, page 17, heading 5).

In response, this is not one of the grounds for enablement rejection currently on record, and thus the arguments are moot.

It is noted the lack of enablement issue here is that whether one can obtain the homozygous knockout animals without undue experimentation.

§ 1.132 Declaration by Dr. Ian Wilmut

The appellant asserts the declaration provides further support of appellant's position that the claimed invention is enabled by the application as filed.

Dr. Wilmut submitted, along with the declaration, a publication he co-authored with *Rhind et al* which presented an investigation showing various lung histological abnormalities that occurred in cloned animals. Dr. Wilmut concluded the lung abnormality is not attributable to the use of genetically modified cells, but is an artifact of the cloning process. Dr. Wilmut goes on to extrapolate that the failure of the α(1,3)GT knockouts was not attributable to the genetic modification, rather, it reflects the rate of failure in this series of experiments, irrespective of what genetic modification were made.

In response, indeed, the *Rhind* reference has shown that genetically manipulated cloned animals do not have higher fatal incidence of lung vascular disease compared to cloned animals without genetic manipulation. The study confirms the cloning process but not necessarily a genetic modification contributing more prominently to the death of the cloned fetus. It however does not negate cloning itself that may cause the failure to obtain homozygous α(1,3)GT knockouts. In fact, *Rhind et al* conclude, "THE HIGH PROPORTION OF CLONES THAT FAIL IN UTERO AFTER NUCLEAR TRANSFER, AND THE HIGH PERCENTAGE OF DEFECTS PRESENT IN THOSE WHICH SURVIVE THROUGH PREGNANCY, SUPPORTS THE IDEA THAT THE NUCLEAR TRANSFER PROCEDURE ITSELF BRINGS ABOUT THESE DEVELOPMENT DEFECTS" (mid-column, page 745)

As to the rate of failure, *Rhind et al.* teaches, "TO DATE, MOST CLONING DEFECTS HAVE BEEN VIEWED AS ISOLATED INCIDENTS...OUR DETAILED ANALYSIS OF LATE-CLONE DEFECTS HAS REVEALED MANY DIFFERENT TYPES OF DEFECTS, SOME OF WHICH HAVE PARALLELS WITH CONGENITAL HUMAN DISEASES" (2nd paragraph, page 744). Apparently, the rate of failure is not an isolated incident, thus the Office maintains instant disclosure fails to provide an enabling disclosure because it fails to teach how to overcome the hurdles known in the art as set forth *supra* whether it is caused by genetic modification or by cloning technology.

Dr. Wilmut then states there is no reason why genetically modified animals cannot be made according to the method of Keith Campbell described in our patent disclosure, and concluded "it is my believe that culture cell lines such as those used by Denning et al. will successfully generates cloned animals after sufficient persistence". He continued by referring to the post-filing publications of *Phelps et al, Kolber-Simonds et al, and Kuroiwa et al* as the support for his believe.

In response, since cloning with the cell lines used by *Denning et al* (Nature Biotech) has not been materialized for production of a homozygous α (1,3)GT knockout ovine, the Office can not evaluate the enablement solely based on the *believe*, rather the Office turn to the factual evidence in the cited post-filing publications for additional information. To this end, *Kuroiwa et al, Phelps et al,* and *Denning et al* (Cloning & Stem Cells) all teach that further development of the cloning technology is necessary for the success of cloning a α(1,3)GT-/- animal. Since the instant specification fails to teach the innovative approaches taught by *Phelps et al, Kolber-Simonds et al, and Kuroiwa et al,*

a reasonable conclusion was reached after weighing many factual considerations that the specification fails to provide the information necessary for success in ovine.

Dr. Wilmut goes on to state "the cloning method used by all these groups is the same as described by Campbell and Wilmut patents. There is no modification to any aspect of our method".

In response, this statement is contradictory to his position in *Rhind* reference, wherein *Rhind et al* concluded with emphasis "THE RESULTS ALSO EMPHASIZE THE NEED FOR BASIC STUDIES ON SOMATIC CELL REPROGRAMMING TO IMPROVE SUCCESS RATES AND REDUCE NEONATAL DEATHS IN CLONED ANIMALS" (Page 745, highlight). The cited conclusion is also contradictory to the teaching of *Kuroiwa et al*, who named the approaches of *Phelps* and his own work as innovative, this conclusion is also contradictory to the publication of *Denning and Clark*, who calls for further development in somatic cell targeting and cloning technology, "WE EXPERIENCED SIGNIFICANT PROBLEMS IN ISOLATING POPULATIONS THAT COULD BE USED FOR NT" (last paragraph, page 229), "THEREFORE, IT IS DIFFICULT TO IMAGINE HOW IT WILL BE POSSIBLE TO ISOLATE SUCH LINES FROM NORMAL PIG FIBOBLASTS SUCH AS THESE WITH THE FREQUENCIES OF GENE TARGETING THAT WE REPORT" (1st paragraph, page 230), and "THERE IS CLEARLY A NEED TO POTIMIZE AS WELL AS DEVELOP NEW APPROACHES IN BOTH SPECIES" (last paragraph, page 230). At the least, *Phelps* employed a new selection method, which was not taught by *Campbell* patent or instant specification, "BECAUSE WE USED THIS POWERFUL SELECTION METHOD, WHICH ALLOWS US TO ISOLATE ANY EVENT THAT RESULTS IN LOSS OF α1,3GT ACTIVITY, WE DISCOVERED A MUTATION IN THE SECOND ALLELE OF THE α1,3GT GENE. HAD WE USED STANDARD SELECTION METHODS WITH PUROMYCIN OR HYGROMYCIN, WE WOULD NOT HAVE FOUND THE MUTATION" " (right column, page 413, emphasis added). *Kuroiwa et al*

also disclosed a new approach that rejuvenates the cell lines by cloned fetuses. Apparently, the art of record evidenced the cloning technology originated from the Campbell and Wilmut patent has undergone significant development.

In assessing the weight to be given an expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex Parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1 182, 25 USPQ2d 1561, (Fed. Cir. 1993).

In the instant case, considering the factors set forth *supra*,

(1) The nature of the fact sought to be established is whether or not the claimed ovine cells and animal homozygous for inactivation of α1,3GT are readily available to the public, whether one could use a heterozygous ovine cell provided in the specification to produce a α1,3GT-/- cell or animal without undue experimentation. The answer is negative due to the challenges presented in failed attempts to knockout the second allele of the α1,3GT, and in the somatic cell NT cloning.

(2) The strength of opposing evidence is strong (See discussion in the rejection and response to arguments *supra*).

(3) Regarding the interest in the outcome of the case, it is noted that Dr. Wilmut is employed by the same institution as the appellant.

(4) Finally, with regard to the presence or absence of factual support for the expert's opinion, it is noted that while Dr. Wilmut's declaration presented general argument that genetic modification itself does not affect cloning with supporting scientific evidence, it does not address the fact that knocking out the second allele of the α1,3GT was not routine in the art, and the investigation was not conducted on α1,3GT knockout ovine animal. In fact, the *Rhind* reference submitted with the declaration supports the Office position that cloning process awaits further refinement. Other assertions in the declaration concerning whether undue experimentation is required appear to contradict the cited art of record.

In view these considerations, the declaration is insufficient to overcome instant rejection in view of numerous cited teachings of record, including the appellant and Dr. Wilmut's own post-filing publications.

The rejection of Claim 16:

The appellant argues that the xenorejection could be resolved by other means such as immune suppression. Appellant cited art of record for xenogeneic heart valve replacement surgery as supporting evidence.

In response, as an initial matter, the claimed method is not directed to just any xenogenic transplantation, but for xenogenic tissue lacking Gal α (1,3)Gal determinants, thus the response citing other xenogenic transplantation is not really addressing the rejected subject matter. Nevertheless, it is noted that the heart valve in the cited references were treated with glutaraldehyde or buffered acid formaldehyde to eliminate the antigeneicity of the tissue, this can be done in a thin tissue layer such as heart valve as described in the articles. This cannot be done for a whole organ or a larger tissue, where the function of the organ and tissue may be depleted by such fixation and preservation.

What the appellant has not and cannot argue is that the starting materials required for practice the claimed invention of claim 16 have yet to become available years after the effective filing date, thus, the skilled intending to practice the invention has to first carrying out undue experimentation to make the required homozygous knockout sheep.

As to the immune suppression therapy, it is noted that the skilled in cited reference (*Platt et al*) is fully aware of the immune suppression therapy known in the art. Therefore, when *Platt et al* (Nat Biotech 2002;20:231-2) concluded, "UNFORTUNATELY, SOLVING THE PROBLEM OF HYPERACUTE REJECTION DOES NOT MAKE XENOTRANSPLANTATION FEASIBLE, BUT RATHER REVEALS A MORE VEXING PROBLEM CALLED ACUTE VASCULAR REJECTION" in a prestige journal at a post-filing date, it implies that the routine immune suppression could not overcome the immune rejection mounted by a host against xenogenic organs.

In conclusion, the Office has properly applied the methodology for determining the sufficiency or lack thereof for enablement of the claimed invention as set forth under 35 U.S.C. § 112, 1st paragraph, and established the claims on appeal lack sufficient enablement commensurate with the scope.

The Rejection under 35 U.S.C. § 101

The appellant asserted that all the arguments under this section are essentially enablement rejections, citing *Nelson v Bowler* arguing identifying a pharmacological activity relevant to an asserted use provides an immediate benefit to the public.

In response, the instant situation is not analogues to *Nelson v Bowler*, where a compound is available and a pharmaceutical activity of the compound has been identified. The instant disclosure fails to provide any material that could be used as a pharmaceutical, thus the enablement (prospect) of making such material has to be evaluated before one can assess the substantial utility and credibility of the asserted utility.

The appellant then argue that the claimed heterozygous cells, fetus, and animal all have utility for further knocking out the second allele or cross-breeding, the argument is partially moot in view of the modification of the ground of rejection, and the remain applicable argument has been addressed in the body of the rejection, and will not be reiterated here.

In conclusion, the Office has properly applied the methodology for determining whether the claimed invention has a substantial and well established utility as set forth under 35 U.S.C. § 101, and established the claims on appeal lack such, and the asserted utility does not appear to be credible.

For the above reasons, it is believed that the rejections should be sustained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,

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